Remarks

Claims 1-5, 9 and 20-24 are currently pending in this application. All claims stand rejected. The claims are to be amended as set forth herein. All amendments are made without prejudice or disclaimer. Reconsideration is respectfully requested in view of the amendments and remarks herein.

1. Restriction Requirement

Applicants note with appreciation that the prior art search has been extended to cover Group II that reads on the peptide of claim 1, wherein X is an arginine residue identified by SEQ ID NO: 5 and that Group II, claims 1-5 and 9 are being examined along with the elected Group I, claims 1-5, 9 and 24.

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2. Drawings

The drawings were objected to because the lines, numbers and letters are not uniformly thick and well defined, and the numbers and reference characters are not plain and legible. Applicants submit herewith, under separate cover, better quality copies of the drawings and request reconsideration and withdrawal of the objections.

3. Preliminary Amendment

The Preliminary Amendment to Table 1 filed January 21, 2000 has not been entered. Applicants submit herewith a clean version and marked up version of the Specification which includes a revised Table 1 to include appropriate SEQ ID Nos. Reconsideration and entry of the amendments to Table 1 is requested.

4. Information Disclosure Statement

Applicants note that the International Search Reports submitted with the application and noted on a PTO 1449 were previously considered by the Examiner, but that the International Search Report was not considered appropriate for an IDS. Applicants submit herewith a new PTO 1449 and copies of the previously disclosed references. Applicants request that the Examiner initial the PTO

1449 and return a copy of the same to the applicants.

5. Objections to the Disclosure

The disclosure was objected to because of informalities. Applicants have amended the specification as suggested by the examiner and request that the objection be withdrawn. Pursuant to 37 C.F.R. §§ 1.121 and 1.125 (as amended to date) please enter the substitute specification in clean form and including paragraph numbers **[0001]** through **[0058]** attached hereto as Appendix B. A marked-up substitute specification to clearly identify amendments to the specification as required by 37 C.F.R. § 1.121(b)(3)(iii) is attached hereto as Appendix C.

Further, applicants submit herewith a substitute Sequence Listing incorporating SEQ ID NO: 17 which was inadvertently omitted from the original Sequence Listing. Applicants request that the ~~substitute Sequence Listing submitted herewith be~~ incorporated into the specification in place of the existing Sequence Listing.

6. 35 U.S.C. §112

Claims 1-5, 9 and 20-24 stand rejected under 35 U.S.C. §112, first paragraph, because the specification while being enabling for certain peptides was not thought enabled for all peptides.

Claims 1-5, 9 and 20-24 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not thought to be sufficiently described in the specification so as to reasonably convey that the inventors had possession of the claimed invention at the time the application was filed.

Further, claims 1, 2, 4-5, 9 and 20-24 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for assertedly failing to define the metes and bounds of a peptide "having similar functional or immunological properties."

Applicants have amended claim 1 to recite "a peptide <u>having up to 15 amino acids</u>" and amended claim 2 to recite "an immunogenic <u>peptide having up to 15 amino acids</u>". Similarly, claim 9 was amended to recite "an analog of a peptide <u>having up to 15 amino acids</u>". Support for the amendments may be found in the Specification, for example, on page 6, lines 31-32. Applicants submit that the Specification is enabled and sufficiently describes peptides having up to 15 amino

acids as further defined by the claims.

Applicants respectfully disagree with the suggestion that the Specification lacks adequate description of the term "derivatives thereof having similar functional or immunological properties." (Paper No. 10, page 4). The Specification discloses that peptides functionally and/or immunologically related to the claimed sequences may be produced and "such peptides (which can include left or right turning residues)" can be "designed and/or generated by various methods known in the art such as peptide synthesis and replacement mapping, followed by functional binding studies." (Specification, page 10, lines 8-14).

The Specification also discloses that the claimed peptides may be synthetically manufactured. Additionally, a derivative functionally and/or immunologically related thereto, retaining the same biological properties as the peptide in kind, not necessarily in amount, can also be manufactured synthetically (*i.e.*, by making deliberate amino acid substitution on the basis of similarity in polarity, charge, solubility, hydrophobicity, and/or the amphipathetic nature of the residues) or can be identified naturally in a manner as disclosed in the Specification. (Specification, pages 14-17, Figure 4). Thus, it is understood that one of skill in the art could, for example, use a combination of deletion and functional binding studies (*e.g.* HLA-A2.1 binding assays) to determine critical HLA-A2 binding residues in the above mentioned peptides, or in a functional derivative thereof. Similarly, analogs which are antagonists for the activity of T cells recognizing the above mentioned peptides (*i.e.*, mHag HA-1 antigen) are also within the skill of the art, given the disclosure in the Specification. Accordingly, claims 1-3, 9 and 20 are sufficiently enabled and described in the Specification.

With respect to claims 4, 5 and 21-24, it was further stated that the Specification lacks *in vivo* working examples as to whether a "vaccine" or a "pharmaceutical composition" comprising the immunogenice polypeptide, derivative thereof, or analog thereof would prevent Graft versus Host disease or would be able to treat HA-1 related autoimmune disease. However, with this statement, the Office fails to acknowledge what is actually being claimed (*i.e.*, a vaccine comprising an immunogenic polypeptide and a pharmaceutical composition comprising an immunogenic polypeptide), and is instead focusing on what the claimed composition might be used for, in this case, preventing GvHD or treating HA-1 related autoimmune disease. Such a position directly

contradicts the M.P.E.P. where it is stated that "[l]ack of a working example . . . is a factor to be considered . . . .[b]ut because only an enabling disclosure is required, applicant need not describe all actual embodiments". M.P.E.P. § 2164.03.

Applicants respectfully submit that claims 4, 21-22 and 5, 23-24 are directed to a vaccine and a pharmaceutical composition comprising an epitope according to the invention, respectively and are not directed to the use of a vaccine or a pharmaceutical composition comprising an epitope according to the invention for the treatment of a HA-1 related immune disease. Thus, claims for a vaccine and pharmaceutical formulation should not require verification for disease treatment. Furthermore, as applicants disclose for the first time, an epitope relating to the mHag HA-1 antigen, and as methods of preparing a vaccine or a pharmaceutical formulation comprising an epitope are state of the art, it follows that a person skilled in the art is now capable of preparing a pharmaceutical composition comprising an epitope of the invention.

The claimed vaccine and pharmaceutical formulation are adequately enabled. Applicants should not be discriminated against based upon the fact that they are at an early stage in the development of a pharmaceutical product. *Cf. Cross v. Iizuka,* 753 F.2d 1040, 1051, 224 U.S.P.Q. 739,747-48 (Fed. Cir. 1985), *In re Brana,* 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). ("Were we to require Phase II [FDA] testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many areas such as the treatment of cancer").

By focusing on one potential use of the composition/formulation, the Office is not considering the enablement of the vaccine compositions themselves, which are the subject of claims 4, and 21-22. Those claims are drawn to "vaccines," which, as is well known to those of skill in the art are compositions used to stimulate an animal's immune response to a particular immunogen. As disclosed in the Specification, the Minor Histocompatability antigens (mHag) can be recognized by alloreactive (immunocompetent) T cells in the context of major Histocompatability complex molecules. In transplant situations where tissue donor and recipient are matched for human leucocyte antigens (HLA), mH antigens may trigger strong cellular immune responses (Specification, pages 1-5). The immunodominant mH HA-1 is the only known human mH antigen that is correlated

with the development of GvHD after BMT (Specification, page 18, lines 16-18). Applicants disclose for the first time amino acid sequences relevant to the mHag HA-1 antigen (Specification, page 5, lines 28-33), which can be functionally presented to the immune system in the context of the HLA-A2.1 molecule (Specification, page 6, lines 24-36).

The Specification teaches that immunodominant mH HA-1 induces HLA-2.1 restricted CTLs *in vivo* and are exclusively expressed on hematopoietic cells, including leukemic cells and leukemic precursors, but not on fibroblasts, keratinocytes, or liver cells (Specification, page 19, lines 7-12). The *ex vivo* generation of mHag HA-1 specific CTLs from unprimed mHag HA-1- and/or HA-2 negative healthy blood donors was demonstrated. HA-1 synthetic peptide-pulsed dendritic cells (DCs) were used as antigen-presenting cells (APC) to stimulate autologous unprimed CD8(+) T cells. These CTLs displayed specific cytotoxic activity against mHag-positive target cells (antigen presenting cells like Epstein Barr Virus transformed lymphoblastoid B cell lines (EBV-LCL). No cytotoxicity against mHag-negative EBV-LCL or against autologous cells was observed. The *ex vivo*-generated HA-1 specific CTLs efficiently lysed leukemic cells derived from acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL) patients. No lytic reactivity was detected against nonhematopoietic cells.

The teachings of the specification disclose that HA-1 specific CTLs can be safely transferred to HA-1- positive patients after BMT. The patient's nonhematopoietic tissues are spaced, resulting in a low risk of GvHD (Specification, page 18-22). The ultimate goal for preventing GvHD and HA-1 related diseases is the induction of specific tolerance to host antigens, thereby maintaining favorable aspects of donor immunity. Thus one of skill in the art, given the fact that an epitope pertaining to the HA-1 antigen has been disclosed for the first time, can not prepare a vaccine or a pharmaceutical composition comprising said epitope which serves as a target for T-cell immunotherapy, relating to GvHD and HA-1 related diseases. Accordingly, applicants submit that claims 4, 5 and 21-24 are enabled and adequately described in the Specification.

7. 35 U.S.C. §102

Claims 1-2 and 9 stand rejected under 35 U.S.C. §102(b) as being anticipated by Nagase et al. ("Nagase").

Applicants respectfully submit that Nagase fails to teach every element of claims 1, 2 and 9. Specifically, Nagase fails to disclose the sequence VLXDDLLEA. Furthermore, even assuming, Nagase disclosed the sequence in the alignment, as suggested, (Nagase, Figure 2, page 323, or Figure 4, page 326) a sequence present in an alignment is not an "isolated" peptide constituting a T-cell epitope obtainable from the minor Histocompatability antigen HA-1. Thus claims 1-2 and 9 avoid Nagase.

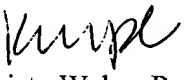
Claims 1-2, 4-5, 9, 21 and 23 stand rejected under 35 U.S.C. §102(b) as being anticipated by Haan et al. ("Haan").

Applicants respectfully submit that Haan fails to disclose every element of claims 1-2, 4-5, 9, 21 and 23. Haan discloses non-isolated peptide sequences pertaining to a different minor Histocompatability antigen as compared to the present invention. Haan discloses a human mHag HA-2 (Haan, page 2683), first column, second paragraph, and Figure 4A) and does not disclose an isolated peptide sequence of the present invention which relates to an isolated minor Histocompatability antigen HA-1. Thus claims 1-2, 4-5, 9, 21 and 23 avoid Haan.

Conclusion

Claims 1-5, 9 and 20-24 are believed to be in condition for allowance, and an early notice thereof is respectfully solicited. Should additional issues remain which might be resolved by a telephone conference, the Office is respectfully invited to contact Applicant's undersigned attorney.

Respectfully submitted,



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March 4, 2002

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APPENDIX A

VERSION WITH MARKINGS SHOWING CHANGES MADE

1. (Twice amended) A peptide having up to 15 amino acids constituting a T-cell epitope obtainable from the minor Histocompatibility antigen HA-1, said peptide comprising the sequence VLXDDLLEA [(SEQ.I.D. No. 1)]SEQ ID NO:1 or a derivative thereof having similar functional or immunological properties, wherein X represents a histidine or an arginine residue.

2. (Twice amended) An immunogenic polypeptide having up to 15 amino acids obtainable from the minor Histocompatibility antigen HA-1, said immunogenic polypeptide comprising the sequence VLXDDLLEA [(SEQ.I.D. No. 1)]SEQ ID NO:1 or a derivative thereof having similar ~~functional or immunological properties, wherein X~~ represents a histidine or an arginine residue.

9. (Twice amended) An analog of a peptide having up to 15 amino acids constituting a T-cell epitope obtainable from the minor Histocompatibility antigen HA-1, said peptide comprising the sequence VLXDDLLEA [(SEQ.I.D. No. 1)]SEQ ID NO:1 or a derivative thereof having similar functional or immunological properties, wherein X represents a histidine or an arginine residue, which analog is an antagonist for the activity of T cells recognizing said peptide.